REMARKS

The Office Action dated June 1, 2004 has been carefully reviewed and the foregoing amendment and the following remarks are made in response thereto. In view of the amendment and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Applicants respectfully submit that no prohibited new matter has been introduced by the amendment. Support for the amendments to the claims can be found in the original claims, figures and throughout the specification as originally filed. Support for amended claims 22, 43, and 64 can be found on pages 29-31 of the specification. For, example, support for the language of a "membrane potential dye" can be found on pages 30-31 (Examples 2-4) and original claim 28. Claims 1-21, 25, 27, 46, 48, 68, 70, 72 and 83-102 have been canceled. As amended, claims 22-24, 26, 28-45, 47, 49-67, 69, 71, and 73-82 are current under consideration.

Summary of the Office Action

1. The Table in Figure 17B has been objected to as not being in compliance with 37 C.F.R. 1.52(b) with respect to the font size.

2. Claims 1-11 and 15-85 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

3. Claims 1-9, 12, 13, 15-27, 22-49, 54-62, 64-70 and 76-85 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Ballyk *et al.* (WO 98/58074).

4. Claims 28-32, 49-53, 63, and 71-75 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ballyk *et al.* (WO 98/58074).

5. Claims 1-13 and 15-85 have been rejected under 35 U.S.C. § 103(a) as being

unpatentable over Ballyk *et al.* (WO 98/58074) in view of Scott *et al.* (Biochemistry 37, 1998).

Response to the Office Action

Objection to the Drawings

The Examiner has objected to Figure 17B as not being in compliance with 37 C.F.R. 1.52(b). Applicants will submit a corrected version of Figure 17B and respectfully request the withdrawal of this objection.

Rejection of claims 1-11 and 15-85 under 35 U.S.C. §112, 1st paragraph

In the Office Action, claims 1-11 and 15-85 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement and containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that the specification fails to (1) adequately describe the genus of mutant CNG channels and (2) provide the guidance needed to alter the particular CNG channel described (SEQ ID No: 2).

As claims 1-21, 25, 27, 46, 48, 68, 70, 72 and 83-85 have been canceled, the rejection of these claims is rendered moot. With respect to claims 22-24, 26, 28-45, 47, 49-67, 69, 71, and 73-82, Applicants respectfully traverse the rejection and note that the present specification (when taken together with the level of skill in the art at the time the application was filed) constitutes sufficient written description to support the instant claims. Applicants further submit that, in contrast to the Examiner's assertion, the present disclosure establishes that the inventors were in possession of the invention defined by the instant claims.

The Examiner cites *University of California v. Eli Lilly and Co.*, 43 USPQ. 2d 1398, (Fed. Cir. 1997) and states that the specification does not provide a representative number of

species within the genus of mutant CNG channels. However, the *Lilly* court, in discussing how to describe a genus sufficiently to meet the written description requirement states, "a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus." *Id.* at 1406. This statement indicates that a sufficient number of representative sequences can define a genus.

Lilly also discusses the number of sequences required to define a genus. For example, in *Lilly*, a single sequence was found not to cover the claimed genera; further, *Lilly* cites *In re Gosteli*, 872 F.2d at 1012, 10 USPQ2d at 1618 (Fed. Cir. 1989), in which the disclosure of two compounds was not sufficient to describe a broader subgenus. These cases suggest that more than two species are necessary to represent a genus. *Lilly* also cites In *re Angstadt*, 537 F.2d at 502-03, 190 USPQ at 218 (CCPA. 1976), in which "the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process." This suggests that a plurality of sequences is sufficient to define a genus.

Applicants have disclosed a number of amino acid sequences of mutant CNGs such as SEQ ID No. 3, No. 5, and No. 7 and many additional mutated CNG channel sequences are in the prior art. Because the specification has a plurality of sequences representing the genus, it meets the criteria discussed in *Lilly* for defining a genus. In addition, these mutants represent common characteristics of the claimed molecules, *i.e.*, improved sensitivity for cAMP. This requirement permits one skilled in the art to readily exclude molecules beyond the scope of the genus.

Furthermore, the PTO's own Revised Guidelines state that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice. As noted above, Applicants have provided description of mutated CNG channels with nucleotide sequences encoding the mutated channels. Applicants submit a representative number of species has been disclosed.

The Examiner then cites *In re Fisher*, 166 USPQ 18 (CCPA 1970) and states, "[b]ecause one of ordinary skill in the art cannot follow the guidance provided by the instant specification and alter a naturally occurring CNG channel protein and predict a particular modification is going to increase the sensitivity of that CNG channel protein to cAMP relative to an unmodified CNG channel, the instant specification is not enabling for the full scope of these claims."

Applicants respectfully traverse. First, one skilled in the art could routinely make and use mutant polypeptides that fall within the scope of claims as amended herein. In particular, methods for producing polypeptides which have specific amino acid sequences are both known in the art and disclosed in the specification. Examples of methods which introduce mutations into a protein include site-directed mutagenesis, PCR, and gene shuffling methods.

Second, contrary to the Examiner's assertions, the specification provides guidance to one of skill in the art as to where the mutation should be made. The specification provides that the mutations could be made in the cyclic nucleotide binding domain, the C-linker region and the NH_2 terminus that enhance the efficacy of cyclic nucleotide to open CNG channels (page 20, lines 14-20). In addition, it is well known in the art that the structure of a channel can be altered to modify the cyclic nucleotide binding affinity. Mutation studies have identified the molecular basis of ion selectivity, including calcium permeability, ligand biding activity and the transmission of ions through the channel. One of skill in the art knows that the molecular basis of channel properties can be exploited in the optimization of these proteins for specific purposes. For example, Warnum *et al.* (1995) (Neuron 15: 619-625), cited in Ballyk *et al.* (WO 98/58074), have demonstrated that the cyclic nucleotide selectivity was significantly altered by the substitution of a nonpolar residue for an aspartic acid residue in the cyclic nucleotide binding domain. Similarly, Scott *et al.*, cited by the Examiner as prior art, were able to rely on structure models of CNG channel to predict four amino acid residues that could interact with the purine

and subsequently made mutations for these amino acids (Biochemistry, 1998 at 17240).

In light of the foregoing arguments, Applicants respectfully submit that the rejection of claims based upon 35 U.S.C. § 112, first paragraph, is overcome and withdrawal of such is kindly requested.

Claim Rejections under 35 U.S.C. § 102(b)

Claims 1-9, 12, 13, 15-27, 22-49, 54-62, 64-70 and 76-85 have been rejected under 35 U.S.C. 102(b) as being anticipated by Ballyk *et al.* (WO 98/58074). Applicants submit that the cancellation of claims 1-9, 12, 13, 15-21, 25, 27, 46, 48, 68, 70, 72 and 83-85 renders the rejection of these claims moot. In an effort to facilitate prosecution and without surrendering any subject matter in this invention, Applicants have amended claims 22, 43 and 64 to further distinguish the claimed subject matter from the cited reference.

Amended claims 22, 43, and 64 recite, *inter alia*, a method of detecting activity of a G protein-coupled receptor by expressing a G protein coupled receptor and a mutant CNG channel in a host cell and measuring the activity with at least one membrane potential dye.

Ballyk teaches the expression of a G protein coupled receptor and an unaltered CNG gene in a host cell. Although the reference suggests on page 7 that the structure of CNG can be altered to change the properties of the channel in terms of ion permeability and cyclic nucleotide binding affinity, nowhere in the Ballyk reference is there any specific teaching of expression of a mutant CNG channel, let alone a mutant CNG channel with increased sensitivity to cAMP.

In addition, Ballyk teaches the use of fluorescence dyes such as Fluo-3-AM to measure calcium influx in a cell. The detection involves pretreatment of the cell with the dye followed by incubation with a buffer (see pages 12 and 19 of the reference). In contrast, the amended claims recite a method of detecting CNG activity using a membrane potential dye. A membrane

potential dye can enter a cell only upon cell depolarization. Therefore, unlike the dye used by Ballyk which passively diffuses into a cell, the entry of the potential dye into a cell can be achieved only when an action potential has been triggered in the cell.

The standard for anticipation under 35 U.S.C. § 102 is strict identity. In other words, anticipation under § 102 can only be established by a single prior art reference that teaches each and every element of the claimed invention. Since Ballyk does not teach a method of measuring ion channel activity in a cell expressing a G protein coupled receptor and a mutant CNG gene with a membrane potential dye, it does not anticipate amended claims 22, 43, and 64, and claims dependent thereon. Applicants respectfully request that the rejection of claims under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections under 35 U.S.C. §103(a)

Claims 28-32, 49-53, 63, 71-75 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Ballyk *et al.* (WO 98/58074). Applicants respectfully traverse. According to MPEP §706.02(j) (Eighth Edition, Revision 2, May 2004), there are three basic criteria which must be met in order to establish a *prima facie* case of obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (Emphasis added).

The reference cited by the Examiner clearly fails to meet these criteria. As discussed above, the Ballyk reference does not teach the expression of a G protein coupled receptor and a mutant CNG channel with enhanced sensitivity to cAMP. Nor does the reference teach or

suggest a method of detection of the activity of the ion channel with a membrane potential dye. Without a teaching or suggestion of all the elements of claims 22, 43, and 64, and claims dependent thereon, a *prima facie* case of obviousness has not been established. Favorable consideration of the Claims in view of the Applicants' remarks is requested.

Claims 1-13 and 15-85 also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over a combination of Ballyk *et al* (WO 98/58074) and Scott *et al.* (Biochemistry 37, 1998). As claims 1-21, 25, 27, 46, 48, 68, 70, 72 and 83-85 have been canceled, the rejection of these claims is rendered moot. With respect to claims 22-24, 26, 28-45, 47, 49-67, 69, 71, and 73-82, Applicants respectfully traverse. With respect to the primary Ballyk reference, the Examiner is directed to the discussions of § 102 rejection above. As indicated, Ballyk does not disclose or suggest a method of detection of ion channel activity with a membrane potential dye. The Ballyk reference also fails to teach co-expression of a G protein coupled receptor and a mutant CNG channel with enhanced sensitivity to cAMP.

The other cited reference, Scott *et al.*, does not provide what Ballyk lacks. Scott is limited to a disclosure of expression a mutant bovine retina CNG in tSA-201 cells or COS-1 cells. Scott does not discuss any method related to Applicant's claimed method comprising co-expressing a G protein coupled a G protein coupled receptor and a mutant CNG channel in a cell, nor does it discuss the use of membrane potential dyes in measuring the ion channel activity.

Accordingly, even if these references were properly combined, the combination of Ballyk and Scott does not provide Applicant's claimed method for detection of G protein coupled receptor activity because neither reference discloses or suggests the step of using membrane potential dyes to measure CNG activity. The 35 U.S.C. § 103(a) rejection of the claims should be withdrawn.

Conclusion

The foregoing remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, he is invited to telephone the undersigned at his convenience.

If there are any fees due in connection with the filing of this amendment, please charge the fees to our Deposit Account No. 50-310. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted
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